REMARKS

With entry of this amendment, the status of the claims is as follows:

Original:	1-13
Currently amended:	14
Previously presented:	None
Canceled:	19-26
Withdrawn:	14-18
New:	None

Claims 1-18 are pending, of which claims 14-18 stand withdrawn. Reconsideration is requested.

The specification has been amended to insert a priority claim after the title. It is noted that the Office acknowledged the priority claim in the filing receipt mailed March 9, 2004.

Claim 14 has been amended to depend from claim 1.

Claims 19-26 have been canceled.

Rejection under 35 U.S.C. § 103

Claims 1-13 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Askin et al. (US5508404). The rejection is traversed.

The claimed invention is directed to a process for the reductive alkylation of cyclic amines with a heteroaryl aldehyde in the presence of a tetrahydroborate salt, wherein the heteroaryl moiety is an N-containing, π-deficient heteroaryl such as pyridyl, quinolinyl, isoquinolinyl, etc. (see the definition of R^1 in claim 1). The tetrahydroborate salt functions as a reducing agent in the reaction. Tetrahydroborate salts (e.g., $NaBH_4$) are attractive reducing agents, because they can be effective over a wide pH range and are inexpensive and non-toxic. By contrast, both $NaBH(OAc)_3$ and $NaBHCN_3$ are very expensive, and $NaBHCN_3$ is toxic due to the presence of cyanide. There is, however, a problem associated with the use of a tetrahydroborate salt as a reducing agent with N-containing π-deficient heteroaryls. As set forth in the application (see page 2, lines 21-24), the π-deficient heteroaryls contain a ring nitrogen in an imine-type structure, the ring nitrogen having a lone pair that is not utilized in the aromatic π system. These ring nitrogens thus have a great tendency to react with electrophiles such as borohydrides and to rapidly form highly stable borane complexes. These complexes can be difficult to cleave, often requiring the use of strong mineral acids which in turn can degrade or remove desired acid-sensitive groups that may be present. The claimed invention solves this problem (see step C in claim 1) by cleaving the complexes using a Pt or Pd catalyst in the presence of an alcohol. Example 1 is an illustration of the claimed process, wherein indinavir is

prepared by the reductive alkylation of indinavir penultimate (Compound **3**) with 3-pyridinecarboxaldehyde in the presence of $NaBH_4$. About 30% of the resulting product is a pyridinyl-borane complex of indinavir. Treatment of the product with PtO_2 and methanol, followed by isolation of product provided a 92% yield of indinavir with a purity of 100% by HPLC. The use of a strong mineral acid to cleave the borane complex of indinavir, which is acid sensitive, would have resulted in a degraded product (see the application at page 2, lines 24-27).

Askin et al. discloses the preparation of indinavir by reductive alkylation of 3-pyridinecarboxaldehyde with indinavir penultimate in the presence of an excess amount of a reducing agent. Askin et al. discloses several suitable reducing agents including $NaBH_4$ (col. 7, line 32), and further discloses that sodium triacetoxyborohydride, sodium cyanoborohydride, and formic acid are preferred reducing agents (col. 7, lines 34-35). However, Askin et al. nowhere teaches or suggests that the reductive alkylation of indinavir penultimate with 3-pyridinecarboxaldehyde using a tetrahydroborate reducing agent can lead to the formation of highly stable borane complexes. There are no examples in Askin et al. of the use of $NaBH_4$. Example 1 of Askin et al. describes the use of sodium triacetoxyborohydride, but nothing in Example 1 indicates that any borane complexes were formed. In fact, $NaH(OAc)_3$ cannot form amine-borane complexes. Amine-borane complexes require three hydrogens on the borane atom, which would typically come from tetrahydroboride salts or diborane. $NaH(OAc)_3$ only has one hydrogen per boron atom. Accordingly, there is no recognition or suggestion in Askin et al. of the problem posed by the formation of highly stable borane complexes. Furthermore, Askin et al. does not otherwise teach or suggest that borane complexes resulting from the use of a tetrahydroborate reducing agent can be successfully cleaved by treatment with Pt or Pd catalysts and an alcohol to obtain indinavir in a high yield and with high purity. In short, there is nothing in Askin et al. that would motivate or otherwise guide the person of ordinary skill in the art to modify the process disclosed therein to reach the claimed process.

Other remarks:

1. The Examiner asserts that the only distinction between the process disclosed in Askin et al. and the claimed process is the number of steps involved (see the Office Action at page 4, the last four lines). That is incorrect. Nowhere does Askin et al. teach or suggest treatment step C recited in claim 1.

2. The Examiner asserts that there is "a reasonable expectation that the resulting product would be pure because Ashkin (sic) discloses that the process is amenable to a variety of solvents." (Office Action, page 5, lines 6-8) A variety of solvents can be employed in the Askin et al. process and a pure product can be obtained. However, it is not the choice of solvent that is of interest, but rather the choice of reducing agent. The fact is that Askin et al. does not recognize that the use of a tetrahydroborate reducing agent can result in the formation of highly stable indinavir-borane complexes that can adversely affect both yield and purity.

3. The Examiner refers to Example 25 in Askin et al. to support his position (Office Action, page 5, lines 8-9). Example 25 discloses the alkylation of indinavir penultimate with picolyl chloride. This is not a reductive alkylation. It is a straightforward alkylation. It is an entirely different chemical route and would provide no guidance or motivation to the skilled artisan with respect to the claimed process.

Based on the foregoing remarks, withdrawal of the section 103 rejection is requested.

Rejoinder of Claims 14-18

Claims 14-18 have been amended to directly or indirectly depend from claim 1 which is believed to be in condition for allowance. Rejoinder of claims 14-18 is accordingly requested.

It is believed that the application is in condition for allowance. The Examiner is asked to telephone the undersigned should any minor matters need to be resolved before a Notice of Allowance can be mailed.

Respectfully submitted,

By: Kenneth R. Walton

Kenneth R. Walton, Reg. No. 32,951
Attorney for Applicants
MERCK & CO., Inc.
P.O. Box 2000
Rahway, New Jersey 07065-0907
Tel.: (732) 594-3462
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